

Guidance for Industry

Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance VICH GL27

DRAFT GUIDANCE

This document is being distributed for comment purposes only

This draft guidance document is an initial step in developing harmonized technical guidance for approval of therapeutic antimicrobial veterinary medicinal products intended for use in food-producing animals with regard to characterization of antimicrobial resistance selection in bacteria of human health concern in the European Union, Japan, and the United States.

Comments and suggestions regarding this document should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
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GUIDANCE ON PRE-APPROVAL INFORMATION FOR REGISTRATION OF NEW VETERINARY MEDICINAL PRODUCTS FOR FOOD PRODUCING ANIMALS WITH RESPECT TO ANTIMICROBIAL RESISTANCE

Recommended for Consultation
at Step 4 of the VICH Process
on 28 June 2001
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-producing Animals with Respect to Antimicrobial Resistance

This guidance represents the Agency's current thinking on the issue described in the title. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations.

Introduction

When evaluating the safety and effectiveness of antimicrobial products for use in animals, regulatory authorities should consider the potential for such antimicrobial agents to select for resistant bacteria. Therefore, guidance is needed for drug sponsors on the type of information that should be reported to the regulatory authorities. This information should help to characterize the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern. The information provided should be used to contribute to an overall assessment of the potential impact of the product on human health.

Objectives

The objective of this draft guidance is to provide harmonized technical guidance in the E.U., Japan and the U.S. for registration of therapeutic antimicrobial veterinary medicinal products intended for use in food-producing animals with regard to characterization of antimicrobial resistance selection in bacteria of human health concern.

For clarification, this guidance outlines the types of studies and data which are recommended to characterize the potential resistance development as it might occur in the target animal under the proposed conditions of use of the product. This includes information which describes attributes of the drug substance, the drug product, the nature of the resistance and the potential exposure of the gut flora in the target animal species. It does not account for post-slaughter factors such as processing of food products or kitchen hygiene that affect the potential human health impact.

Pathogen load studies, ecotoxicity studies, the process for risk assessment, the establishment of Acceptable Daily Intakes (ADIs), and consideration of residues of antimicrobial agents are not included in this guidance. Also, because of principle differences in production systems, bacterial populations present, and potential zoonotic public health threats, fish are not included in this document.

Data recommendations

Information in the subsequent sections has been designated as 'basic' or 'additional' data. Where information is designated as 'basic', sponsors should provide such information.

Where information is designated as 'additional', sponsors may also choose to include some or all of those data. The proposed use conditions of the product, the potential exposure of animal gut flora to the antimicrobial agent, the potential exposure of humans to resistant bacteria or their resistance genes, and the perceived importance of the drug (or related drugs) to human medicine may be factors on which the sponsor provides 'additional' data.

1. Basic information

1.1 Antimicrobial class

This information should be based on the drug substance's chemical structure, patent information, and information that is contained in subsequent sections. For example, the common name, chemical name, CAS (Chemical Abstract Services) registry number, chemical structure, and manufacturer's code number and/or synonyms are recommended.

1.2 Mechanism and type of action

This information may be inferred from literature studies, patent information, or specific mechanism of action studies undertaken by the sponsor. Characterization as to bacteriostatic vs. bactericidal information should be included in this section.

1.3 Antimicrobial spectrum of activity

1.3.1 General data

Information on the antimicrobial drug substance should be provided by the sponsor including data from MIC (minimum inhibitory concentration) tests against a wide variety of microorganisms or from literature studies, in order to determine the overall spectrum of activity. Where MICs are determined by the sponsor, the source of the isolates may be from culture collections, diagnostic laboratories, or other repositories.

1.3.2 MICs of target animal pathogens (as per product label claim)

These data are considered supportive for the purposes of this guidance. Information on target animal pathogen MICs may be obtained from data within the Efficacy section of the dossier.

1.3.3 MICs of foodborne pathogens and commensal organisms

Data should be presented to show MICs of foodborne pathogens and commensal organisms. This information may be based on literature data or on studies done by the sponsor. Based on consideration of the spectrum of activity, appropriate organisms may include:

Foodborne pathogens:

- *Salmonella* spp.
- *Campylobacter* spp.

Foodborne commensal organisms such as:

- *Escherichia coli*
- *Enterococcus* spp.

Relevant bacterial species/serotypes should be isolated from the proposed target animal species. Where possible, MIC values should be determined with a validated and controlled method, such as those described in NCCLS documents (e.g., M31-A, Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria isolated from Animals; Approved Standard).

1.4 Resistance mechanisms and genetics

Where possible, information on the resistance mechanism(s) and information on the molecular genetic basis of resistance to the antimicrobial drug substance should be provided. This information may come from literature or from studies done by the sponsor. Information from related analogs should be provided in the absence of data on the drug substance.

1.5 Occurrence and rate of transfer of resistance genes

Information on the occurrence, or absence, of transfer and rate of transfer of resistance genes should be provided. This information may come from literature or from studies done by the sponsor. Specific studies to evaluate the occurrence of genetic transfer may follow a protocol such as found in Antibiotics in Laboratory Medicine, 4th ed., V. Lorian, ed. 1996. Williams and Wilkins, Baltimore, Maryland.

The sponsor may consider including target animal pathogens, relevant foodborne pathogens, and relevant commensal organisms. Information from related analogs should be provided in the absence of data on the antimicrobial drug substance.

1.6 Occurrence of cross-resistance

Information on cross-resistance to the antimicrobial drug substance should be provided. This information may come from literature or studies done by the sponsor. This should include a phenotypic description and, if available, a genotypic description.

1.7 Pharmacokinetic data

Pharmacokinetic data may be obtained from other sections of the dossier. Data may include the following:

Serum / plasma concentrations versus time data

Maximum concentration (C_{max})

Time of maximum concentration (T_{max})

Volume of distribution (V_D)

Clearance (Cl)Area under the concentration-time curve (AUC)

Bioavailability [(AUC formulation/AUC iv) x 100]

Protein binding

Pharmacokinetic / pharmacodynamic data with a particular view to anticipated drug substance concentrations in the intestinal tract

2. Additional information

Sponsors may also choose to include some or all of the following:

2.1 *In vitro* mutation frequency studies

In vitro mutation frequency studies involving test organisms may follow a protocol such as found in Antibiotics in Laboratory Medicine, 4th ed., V. Lorian, ed. 1996. Williams and Wilkins, Baltimore, Maryland.

2.2 Occurrence of co-resistance

Information on co-resistance of the antimicrobial drug substance in question with other antimicrobial agents may be provided by literature information or studies done by the sponsor. This should include a phenotypic description and, if available, a genotypic description.

2.3 Antimicrobial drug activity in gut

Where available, details may be provided on the concentrations of microbiologically-active compound which might be expected to occur within the intestinal tract contents or the faeces when the antimicrobial drug product is administered according to the proposed conditions of use. The activity in question may be due to the parent antimicrobial drug substance, or to active metabolites.

Where such data are not available, details may be provided by metabolism studies relevant to the gastrointestinal tract. Data from metabolism studies may be obtained from other sections of the dossier.

2.4 Other animal studies

The sponsor may choose to include information from other animal studies conducted to help characterize the rate and extent of resistance development associated with the proposed use of the antimicrobial drug product. This may include data from clinical studies conducted in support of other sections of the dossier.

The predictive value of the results of such studies is yet to be established with regards to resistance development. Therefore the results of such studies should be interpreted in the context of all other pre-approval information described in this document.

2.5 Historical information

When available and relevant, historical information from literature or studies on previously approved uses of the drug product or related products may be provided.

3. Discussion

The sponsor should discuss the information provided in the previous sections in terms of the exposure of foodborne pathogens and commensal organisms to microbiologically active substance in the target animal after administration of the veterinary medicinal product under the proposed conditions of use, and the potential for resistance selection in such bacteria.

Glossary

Antimicrobial agent: a drug substance that is either biologically derived or chemically produced with antibacterial effect as its major therapeutic effect

Food-producing animals: In this guidance, cattle, poultry and pigs are considered as major food-producing animals. Because of regional differences, in some countries other animal species including, but not limited to sheep, goats, ducks and rabbits may be considered as major food-producing animals.

Therapeutic antimicrobial veterinary medicinal product: an antimicrobial drug product used in the prevention or treatment of bacterial disease. This excludes antimicrobial agents only intended for growth promotion.

Antimicrobial drug substance: active ingredient of the antimicrobial veterinary medicinal product

Target animal pathogen: pathogenic bacterial species causing infection in the target animals for which the veterinary antimicrobial medicinal product is indicated to be used for, as claimed on the label.

Foodborne pathogens: zoonotic bacterial species, of which animals could be carriers in the intestinal content, that could be transmitted to humans by the food chain and subsequently cause foodborne infections in humans.

Commensal organism: bacteria living in or on animals but not considered animal pathogens.